canceled subject matter in one or more continuing applications. Claims 2-7, 9, 13 and 19 are amended and claims 46 and 47 are added.

The amendments to the specification are supported by the Declaration and Power of Attorney and the original specification. The amendment on page 1 adds the priority statement asserted in the Declaration and claims priority to the filing date of the provisional application. The amendment on page 13 of the specification corrects one typographical error to delete reference to the AAV Rep mutant, Rep-64^{LH}65^{TM}, because this mutant does not result in any AAV replication. Reference to Rep-64^{LH}65^{TM} was inadvertently not deleted from the specification on page 13, line 3 during the preparation of the application. The examiner is referred to Figure 11 which clearly shows that there is no band at "md>" for Rep-64^{LH}65^{TM}. The designation of "md>" indicates the level of AAV replication for each of the specific Rep78 mutants designated at the top of this figure. In the detailed description of the drawings on page 11, lines 5-6, it is recited that "Figure 11 shows that FLAG-77^{LG} replicates at higher levels and that FLAG-192^{HG} replicates at slightly depressed levels compared to wild-type." A review of Figure 11 shows that the one band that is darker and larger in Figure 11 is at "md>" for FLAG-77^{LG} as compared to FLAG-192^{HG}. The wild-type is pSM620/Sph in Figure 11. Thus, it also can be seen that there is no AAV replication for FLAG-64^{LH}65^{TM}. It is believed that this explanation provides sufficient support to amend page 13, line 3 of the specification.

The support for the amendments to the claims can be found in the original claims and the specfication. Amended claim 2 corresponds to original claims 2 and 3. The insertion of the term "corresponding" makes clear that the AAV Rep 78 mutant comprises an AAV Rep 78 modified protein that binds in a specific manner as compared to binding of the corresponding or wild-type AAV Rep78 protein from which it was derived. Further, page 2, lines 2-8 of the specification shows the designation of specific mutant AAVs that contain the AAV Rep78 modified protein as compared to the wild-type AAV Rep78 protein from which it is derived. Further, page 19, lines 15-21 disclose that the AAV Rep 78 mutants were prepared by mutating a wild-type AAV Rep78 DNA sequence that encodes the wild-type AAV Rep 78 protein. Claims 4, 5, 6 and 7 are amended to clarify that the AAV Rep78 modified protein contained in the AAV Rep 78 mutant has the specified binding DNA function as compared to the wild-type AAV Rep78 protein. Support for this language is found throughout the specification, and particularly on page 11, lines 26-29, that shows that

the specification utilizes these terms interchangeably. The specification discloses that the AAV Rep 78 mutants contain a modified AAV Rep 78 protein and both the mutant and the corresponding protein have the modified binding as compared to the wild-type AAV Rep 78 protein from which the modified protein was prepared. Claim 9 is amended to include the SEQ ID NO for the promoter region of HPV-16. Support for this is found in Figure 2 of the application which contains the nucleotide sequence for the HPV-16 promoter. Amended claim 13 is written in independent form and corresponds to original claims 13 and 2, and additionally contains the phrase "... and that results in AAV DNA replication and/or AAV virion production, ..." to clarify this special technical feature. Support for this phrase is found in original claim 4 and on page 12, lines 27-30 of the specification. New claim 46 corresponds to amended claim 2 and additionally contains the phrase "... results in AAV DNA replication and/or AAV virion production, ..." to clarify the special technical feature. Support for this phrase is found in original claim 4 and on page 12, lines 27-30. New claim 47 corresponds to original claim 3. No new matter has been added.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-20 are rejected by the Examiner as allegedly being indefinite. The Examiner alleges that claim 1 is unclear regarding whether "modified protein" means a protein with an insertion, deletion, or substitution, or N and/or C-terminal substitutions. Applicants have canceled claim 1 and believe that the Examiner's objections to specific language is now obviated. In regard to the lack of clarity issue raised in regard to the "wild-type protein," which is present in the pending claims, applicants point out that the specification discloses that the wild-type AAV Rep 78 protein is a non-mutated AAV Rep 78 protein from which the modified AAV Rep 78 proteins are derived. The specification supports this statement on page 19, line 15 to page 20, line 6 and page 2, lines 2-8. Page 19 provides a reference to sequences of AAV Rep 78 DNA and amino acid sequences as examples that are known to persons skilled in the art. The specification discloses modifying specific sequences of these known sequences to obtain the AAV Rep 78 mutants that contain the AAV Rep 78 modified protein. Claim 2 has been amended to read "adeno-associated virus" instead of AAV as requested by the Examiner.

The Examiner alleges that the "bind differently" phrase of claim 2 is indefinite. Applicant points to page 12, lines 11-13 and 23-26 which states that the AAV Rep78 mutants either possess enhanced or weakened DNA binding to other viral DNA as compared to the

wild-type AAV Rep78 protein's binding to the same viral DNA. Further, the specification discloses assays that measure and compare the binding affinities of the AAV Rep 78 mutants containing a modified AAV Rep 78 protein as compared to the corresponding wild-type AAV Rep 78 protein. See the specification on pages 9-11 in the description of Figures 3, 4, 12 and 13, on pages 18-19 in the description of the EMSA and on pages 22, 23 and 26 describing the experiments and results that generated these figures. Particularly, page 26, lines 19-27 discloses the comparison of the binding of a AAV Rep 78 mutant containing an AAV Rep 78 modified protein to wild-type AAV Rep 78 protein. Further, the Examiner alleges that claim 2 is unclear as to whether the invention is the AAV Rep78 mutant or an AAV Rep78 modified protein. Applicant further points to page 11, lines 20-22 which states that the invention is directed to AAV Rep78 mutants that contain a modified AAV Rep78 protein as opposed to the wild-type AAV Rep78 protein. Claims 2, 4-7 and 13 have been amended to clarify this issue.

The Examiner alleges that claim 6 is not clear as to the meaning of "combination thereof." Applicant points to page 13, lines 4-8 where the specification explains that the wild-type AAV Rep78 protein may be modified by truncating the protein, substituting amino acids, deleting internal amino acids, or a combination of those three modifications. For example, the wild-type Rep78 protein can be modified by substituting one amino acid for another amino acid and deleting an additional amino acid from the middle or the end of the sequence as well. This language is well recognized patent terminology that has a legal meaning, and it is requested that this rejection be withdrawn.

The examiner believes that claim 7 is not clear as to location or size of the "minimum number of amino acids" of the wild-type AAV Rep78 protein that are necessary to bind to the desired DNA sequences. The applicant points out that a specific number and location of amino acids of the wild-type AAV Rep78 do not need to be recited in the claim. The specification provides assays to determine binding of the AAV Rep 78 proteins to DNA sequences as discussed above. Thus, a person of skill in the art would be able to determine through trial and error experimentation the minimum number and location of amino acids that are necessary to bind to the DNA sequence to obtain enhanced inhibition of papillomavirus or an oncogene. Further, in this regard, page 14, lines 11-13 of the specification state that such methods of testing of the binding would not require undue experimentation and are disclosed in the invention or are known to person of skill in the art. Additionally, page 21, lines 18-25

of the specification discloses an assay for testing whether the modified AAV Rep78 protein has weakened or strengthened binding capacity. Applicants contend that this explanation with reference to assays in the specification provide adequate information to withdraw this rejection.

The Examiner alleges claim 9 is indefinite for not identifying a relevant SEQ ID NO. Applicants point out that SEQ ID NO:4 has been added to claim 9 to clarify the HPV-16 nucleotide sequence. Applicant refers to Figure 2 of the application which provides support for the HPV-16 nucleotide sequence represented in SEQ ID NO:4.

The Examiner alleges that claim 13 has enlarged the scope of claim 1 by including an element, the fusion protein, which has no antecedent basis. Applicants have amended claim 13 so that it is written as an independent claim, and therefore obviates any lack of antecedent basis issues. Applicant directs the examiner to page 14, lines 14-28 of the specification as support for the fusion protein of claim 13.

As with claim 13, the Examiner additionally alleges that claim 19 has enlarged the scope of claim 1. Applicant has amended claim 19 to more clearly recite the components of the composition to overcome this rejection.

In view of the above comments and the showing of support in the specification, it is requested that these rejections be withdrawn with regard to pending claims 2-20.

Rejection under 35 U.S.C. § 102

Claims 1-4, 6, 8, 9, and 11 are rejected as allegedly being anticipated by *Zhan, et al.* ("Zhan"). The Examiner alleges that Zhan is a 35 U.S.C. § 102(a) prior art reference against the applicant. Applicants would like to point out that present application claimed priority in the Declaration and Power of Attorney to the provisional application, U.S. 60/160,608, filed on October 21, 1999. Applicants direct the Examiner to the publication date of the Zhan reference which is October 29, 1999, which was published after the priority date of the present invention. Applicants request that this rejection be withdrawn as the Zhan reference may not be used as prior art against the applicants' invention under 35 U.S.C. § 102(a) as it was published after the provisional application's filing date.

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Srivastava, et al.* ("Srivastava") or *Chiorini, et al.* ("Chiorini"). The Examiner alleges that

these two references anticipate modified AAV Rep78 proteins. Applicants respectfully disagree with the Examiner's interpretation of the Srivastava and Chiorini references. Applicants contend that Srivastava does not disclose a modified AAV Rep78 protein and only discloses the AAV DNA sequence. Specifically, the Examiner is directed to page 559 of Srivastava which says "no viral proteins have yet been identified that are coded for by the transcripts." Pages 559-561 of Srivastava only discloses the possible sizes of the AAV viral proteins with no disclosure of what the proteins are responsible for or any further modification of the proteins. Applicants contend that Chiorini does not disclose the particular modified AAV Rep78 protein claimed in the present invention. Page 18 of Chiorini mentions making minor modifications of the nucleic acid of AAV viral proteins. However, Chiorini further states that such modifications should be "silent mutations in the coding sequences, mutations that make neutral or conservative changes in the encoded amino acid sequence, and mutations in regulatory regions that do not disrupt the expression of the gene." Such minor changes to the DNA encoding for AAV viral proteins in general does not anticipate the more major changes made to the actual amino acid sequence of the AAV Rep78 protein that binds differently to DNA sequences as compared to wild-type AAV Rep 78 as claimed in this invention. The claimed invention is an AAV Rep78 protein that is modified in such a way as to make major changes in its binding capabilities. The minor modifications disclosed in Chiorini do not result in increased or decreased DNA binding as the modifications do in the present invention.

In view of these arguments regarding the differences between the presently claimed invention and Srivastava and Chiorini, it is requested that these rejections be withdrawn.

Claims 13 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being taught by *Batchu, et al.* ("Batchu"). The examiner alleges that Batchu teaches a MBP-AAV Rep78 mutant fusion protein. Applicants have clarified claim 13 and dependent claim 16 to state that the claimed fusion protein containing the AAV Rep78 modified protein results in AAV DNA replication and/or virion production. Applicants contend that while Batchu discloses a MBP-AAV Rep78 fusion protein, such protein does not exhibit the claimed DNA replication and/or virion production. In view of this clarification to claim 13 and the above comments, it is requested that this rejection be withdrawn.

Claims 1 and 2 are rejected under 35 U.S.C. § 102(e) as being anticipated by *Russel, et al.* ("Russel"). The Examiner alleges that Russel discloses and claims an AAV Rep78

modified protein, however, Russel does not disclose an AAV Rep78 modified protein. Applicant asserts that Russel discloses a wild-type AAV replication protein but not any modification thereof. Applicant points to page 19 of the Russel patent which explains that the invention is directed to a "substantially purified polypeptide ... which can be a Rep protein of AAV3B or AAV6." Russel further states that the Rep protein is "characterized in that it has an amino acid sequence that is different from the amino acid sequence of the corresponding polypeptide encoded by AAV2 or AAV3A." Applicant believes that the changes in the amino acid sequences of the Rep78 protein in Russel do not constitute a modification of the wild-type Rep78 protein as claimed in the present invention. Rather, applicant contends that the modifications in Russel pertain only to differences in the wild-type proteins between different AAV strains and not between AAV Rep 78 mutants and wild-type. In view of these comments, the showing of differences between the cited prior art and the claimed invention, it is requested that this rejection be withdrawn.

CONCLUSION

The present response is intended to be a complete response to the Examiner's Office Action. It is believed that the above arguments and amendments to the claims place the application in condition for allowance, and a notice to that effect is respectfully requested. If there are any minor issues which can be taken care by telephone, it is requested that the Examiner contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date June 27, 2002

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MARKED-UP SPECIFICATION:

The second type of AAV Rep78 mutant is a mutant possessing weak or no DNA binding affinity to at least one DNA sequence obtained from a PV or an AAV, such as the promoter, AAV p5 or HPV-16 p97, when this binding affinity is compared to the binding of the wild-type AAV Rep78 protein. Although these mutants bind less strongly, if at all, to the selected DNA(s), these mutants have other functions that are intact, and therefore have enhanced ability to complement AAV functions, that results in the generation of higher levels of AAV DNA replication and/or AAV virion numbers. These increased levels of AAV DNA replication and virions are useful for generating more rAAV for gene therapy as compared to the wild-type Rep78. But these weak or no binding AAV Rep78 mutants, also are useful in treating PV by virtue of the negative impact that the presence of AAV has on the presence of PV. Thus, any mechanisms that would increase AAV numbers is expected to decrease PV. The Rep-77 ^{LG}[,] **and** Rep-79 ^{FA} [and the Rep-64^{LH}65^{TM}] mutants are examples of this type of mutant and are disclosed in the present invention.

MARKED-UP CLAIMS:

2. (Amended) [The] **An adeno-associated virus** (AAV) Rep78 mutant [of claim 1, wherein said] **comprising an** AAV Rep78 modified protein **that** binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene or a HIV differently as compared to the binding of [said] **the corresponding** wild-type AAV Rep78 protein.

4. (Amended) The AAV Rep78 mutant of claim 3, wherein said **AAV Rep78 modified protein** [mutant] having no DNA binding or weak DNA binding to said DNA sequence obtained from at least one of a papillomavirus, an AAV, an oncogene or a HIV that results in the generation of higher levels of AAV DNA replication and virion numbers.

5. (Amended) The AAV Rep78 mutant of claim 3, wherein said **AAV Rep78 modified protein** [mutant] having enhanced DNA binding to said DNA sequence obtained from at least one of a papillomavirus or an oncogene that results in enhanced inhibition of at least one of a papillomavirus or an oncoprotein.

6. (Amended) The AAV Rep78 mutant of claim 2, wherein said **AAV Rep78 modified protein** [mutant] is selected from the group consisting of a truncated wild-type AAV Rep78 protein, a wild-type AAV Rep78 protein containing amino acid substitutions, a wild-type AAV Rep78 protein containing internal amino acid deletions, and a combination thereof.

7. (Amended) The AAV Rep78 mutant of claim 6, wherein said **AAV Rep78 modified protein** [mutant] is a truncated AAV Rep78 protein containing at least the minimum number of amino acids of the wild-type AAV Rep78 protein necessary to bind to said DNA sequence to obtain enhanced inhibition of a papillomavirus or an oncogene.

9. (Amended) The AAV Rep78 mutant of claim 8, wherein said papillomavirus promoter region is nucleotides 14-56 of p97 of HPV-16 **of SEQ ID NO:4**.

13. (Amended) A fusion protein comprising [the] **a wild-type** AAV Rep78 protein or [said] **an** AAV Rep78 **modified protein** [mutant of claim 1] **that binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene**

or a HIV differently as compared to the binding of said wild-type AAV Rep78 protein, and that results in AAV DNA replication and/or AAV virion production.

19. (Amended) A pharmaceutical composition comprising at least one AAV Rep78 mutant **[**or said AAV Rep78 protein**]** according to claim [1] **2 or an AAV Rep 78 protein**, in admixture with a pharmaceutically acceptable carrier.